

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-064**

**Medical Review(s)**

NDA# 21-064

M.O. Review # 3

Date of letter: 1/30/01

Date FDA received: 1/31/01

Date reviewer received: 1/31/01

Date review completed: 5/17/01

Update completed: 7/17/01

**1. General Information**

**Drug name:** DMP 115  
**Generic name:** Perflutren Lipid Microspheres  
**Proposed trade name:** DEFINITY  
**Chemical name:** Phospholipid liposomes with perfluoropropane in saline  
**Status:** Response to Action Letter of August 4, 2000  
**Sponsor:** DuPont Pharmaceuticals  
 331 Treble Cove Road  
 North Billerica MA 01862

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	CONTENT
Amendment (NC)	7-Apr-00	7-Apr-00	8-Apr-00	Meeting Request
Amendment	30-Aug-00	30-Aug-00	31-Aug-00	Pre-meeting Package
Re-submission (N-AZ)	30-Jan-01	31-Jan-01	31-Jan-01	Response to Action Letter
Amendment (BS)	23-Mar-01	27-Mar-01	28-Mar-01	Response to Request for Info.
Amendment (BM)	3-Apr-01	4-Apr-01	4-Apr-01	Response to Request for Info.
Amendment (BS)	16-Apr-01	17-Apr-01	17-Apr-01	Response to Request for Info.
Amendment (BZ)	21-Jun-01	22-Jun-01	22-Jun-01	Response to Request for Info
Amendment (BM)	27-Jun-01	28-Jun-01	28-Jun-01	Response to Request for Info
Amendment (BS)	29-Jun-01	2-Jul-01	2-Jul-01	Response to Request for Info
Amendment (BZ)	9-Jul-01	10-Jul-01	10-Jul-01	Response to Request for Info
Amendment (BM)	9-Jul-01	10-Jul-01	10-Jul-01	Response to Request for Info
Amendment (BM)	10-Jul-01	11-Jul-01	11-Jul-01	Response to Request for Info
Amendment (BM)	11-Jul-01	12-Jul-01	12-Jul-01	Response to Request for Info
Amendment (BM)	12-Jul-01	13-Jul-01	15-Jul-01	Response to Request for Info
Amendment (BZ)	12-Jul-01	13-Jul-01	15-Jul-01	Response to Request for Info

**Dosage Form(s) and**  
**Route(s) of Administration,**

**Directions for Use:**

*... a single dose 10 µL/kg by slow I.V. bolus injection over 30-60 seconds, followed by a 10 ml-saline flush. A second 10 µL/kg dose may be administered to prolong optimal imaging. May also be administered via an I.V. infusion of 1.3 ml added to 50 ml of preservative free saline. The rate of infusion is suggested to be initiated at 4 ml/minute, but should be titrated as necessary to*

*achieve optimal image enhancement.*

**Related Approved Drugs:**

Albunex, Optison

**Related Reviews:**

Statistical Review, Biopharm Review, Chemistry Review, Pharmacology/Toxicology Review

**EXECUTIVE SUMMARY****A. Recommendation:**

It appears at this time that the better contrast due to Definity, as described by the sponsor, does not have a functional correlate. At least, not with the cardiac wall motion, as apparent from the data analyses provided by the sponsor so far.

**B. Recommended Phase 4 studies and/ or risk management steps if approvable**

Other sub-analyses within the sub-set of patients with normal heart could identify potential other trends. If not successful, new trials could explore the potential seen with the normals by studying subgroups of normal subjects or patients with a normal heart.

The sponsor should be encouraged to attempt to respond to the Agency suggestion to try to explain the inconsistency in results between the early trials (DMP 115 – 006 and –007) as stated in the Action letter of August 4, 2000 and perform a complete statistical analysis (including subset analyses) to look for other potential trends.

If not successful, more trials would be needed to obtain data demonstrating the ability of Definity-enhanced US to contribute to the diagnosis of heart disease. One of the most apparent options is to correlate the results of Definity with coronary angiography as the standard of truth for CAD.

**II. Summary of Clinical Findings**

The Action Letter of August 4, 2000 stated that “... before DEFINITY™ can be approved, we request additional documentation that improved assessments of LVEB delineation and LV opacification with DEFINITY™ have clinical usefulness. Such information should include data from additional clinical studies in appropriate clinical settings or data from the literature.” The Action Letter also addressed several minor safety and regulatory issues including the pediatric labeling. The sponsor responded satisfactorily, except for the above efficacy concern.

No literature data was submitted in the latest re-submission nor any results of new clinical studies.

Data for the remaining claim, the diagnosis of wall motion abnormalities, were inconclusive in the original NDA. Only one of two trials showed a marginal benefit. There is no evidence that the source of the discrepancy between the two trials was ever investigated by the sponsor.

However, the Action Letter of August 4, 2000 letter specifically brought attention to this point with a renewed urgency.

Although the sponsor argued that marginal changes in an expected direction may be enough for the claim on cardiac wall motion, that conclusion was made from a cursory inspection of summary graphs. This viewpoint was not supported by results of an analysis based on rigorous and complete statistical evaluation. While a graphical analysis could be helpful, it would be contributory only when rigorous and complete. In general, a conclusion from such a comprehensive analysis does not differ from the statistical treatment of the respective data since both analyses are guided by the same principles.

The graphical evaluations submitted by the sponsor were subjected to an assessment by the Agency and to confirm some of the results a special request was made to the sponsor to submit the imaging results of two separate patient sub-sets, namely, the patients with normal and abnormal heart.

Within margin of statistical error, this sub-set analysis revealed that the DEFINITY™ effect in both trials was limited to patients with a normal heart (by MRI). No advantage of DEFINITY™ was seen in patients with abnormal heart. The medical officer's analysis was based first on graphical analysis submitted by the sponsor as a part of this (third) regulatory cycle and confirmed by the sub-set data submitted in tabular form by the sponsor upon special request. The conclusions by the medical officer agreed with those by the statistician who evaluated the tabulated data.

**APPEARS THIS WAY  
ON ORIGINAL**

## 2. Table of Contents

1. General Information .....	1
2. Table of Contents .....	2
3. Material Reviewed .....	2
3.1 Regulatory Update.....	2
3.1.1 Efficacy.....	2

3.1.2 Safety.....	3
3.1.2.1 Pharmacology and Toxicology Deficiencies.....	3
3.1.2.2 Chemistry Deficiencies.....	4
3.1.2.3 Safety Update.....	4
4. Efficacy.....	8
4.1 Concordance Between Sonocardiography and MRI.....	9
4.1.1 Concordance Between the Two Modalities in DMP 115 – 007.....	10
4.1.2 Concordance Between the Two Modalities In DMP 115 – 006.....	11
4.2 Direct comparison of patients with a normal and abnormal heart.....	12
4.2.1 Normal patients in DMP 115 – 006.....	12
4.2.2 Abnormal patients in DMP 115 – 006.....	13
4.2.3 Abnormal patients in DMP 115 – 007.....	13
4.2.4 Normal patients in DMP 115 – 007.....	14
4.3 Clinical Impact in a Patient With Abnormal Heart.....	15
4.4 Conclusion.....	16
4.5 Trend Assessment.....	16
5. Summation.....	17
6. Recommendation.....	18

### 3. Material Reviewed

This re-submission is comprised of a total of 8 volumes of roughly 400 pages each. Clinical data appeared in volumes 1, 6 and 7, a total of 3 volumes. The re-submission was reviewed in full.

The re-submission was submitted as a response to the action letter of August 4, 2000. The Sponsor's answers to individual items contained in the action letter are addressed below in sequential manner in the same order as they appeared in the action letter. Essence of each FDA request precedes the answers. Detailed reasoning and data analyses can be found later in this review.

#### 3.1 Regulatory Update

##### 3.1.1 Efficacy:

1. The Agency letter stated that *"The application continues to lack sufficient data to validate the use of DEFINITY in the evaluation of cardiac wall motion."* In addition it said that *"... (the re-analysis) did not eliminate the inconsistency between the two studies ..."* The Agency letter requested *"... additional documentation that improved assessment of LVEB delineation and LV opacification with DEFINITY have clinical usefulness."* The need for the latter was noted to assess the benefit in risk-benefit analysis *"Because of the potential risk associated with pulmonary microemboli ..."*

*"Such information should include data from additional clinical studies in appropriate clinical settings or data from the literature."*

No ~~new~~ primary data was provided to validate the use of DEFINITY in the evaluation of cardiac wall motion, and the sponsor did not provide any additional data from the literature in this submission. In the earlier re-submission, the sponsor chose to deal with the request to provide sufficient data to support the wall motion indication by offering an unusual, new analysis of imaging results, which lacks validation at this time. In this re-submission the same analysis was carried a step further into segmental analyses. The sponsor did not address specifically the question of inconsistency between the two trials, but, pointedly, the results in the current analyses can be best explained by the differences in patient populations enrolled in these two trials. In particular, any potential useful change due to Definity, although small, can be accounted for by patients with a normal heart, while no such trend was observed in patients with an abnormal heart.

2.

### **3.1.2 Safety:**

#### **3.1.2.1 Pharmacology and Toxicology Deficiencies**

The Agency letter noted that the activated microbubble upper limits of the particle size distribution lack sufficient manufacturing control to ensure safety of the administered product.

The Sponsor has complied with two of the Agency's specific suggestions regarding the studies on the effect of particle size in animal models. However, both studies should be interpreted with caution as numerous assumptions, made in the design of the trials as well as interpretations of the results, render them not directly clinically applicable. The sponsor reported on both studies requested in Action Letter of 8/4/00.

1. The study in a chronically compromised pulmonary circulation disease model in rats showed no overt toxicity of Definity.
2. Another study assessed the effect of intra-arterially administered Definity on the microcirculation. There was entrapment of Definity microspheres in microvasculature in the spinotrapezius muscle and the lungs apparently filtered the larger microspheres, but the potential clinical impact of these results is unclear at this time. Specific recommendations will be made by the reviewing pharmacologist.

These issues were discussed with the reviewing pharmacologist. Please refer to pharmacology/toxicology review for details.

### **3.1.2.2 Chemistry Deficiencies**

The Agency letter asked to adjust the manufacturing controls to ensure that larger particles are eliminated from the injectable suspension. In addition, it was recommended to explore alternative approaches to obtain and validate . . . . . and provide data to establish that the . . . . . product will be functionally equivalent to the product that has been in the clinical safety study.

The Sponsor complied with the Agency's suggestions and at present there are no CMC issues outstanding. The matter was discussed with the review chemist who found the sponsor in agreement pending validation of the methods by the FDA laboratories. Please refer also to the chemistry review.

### **3.1.2.3 Safety Update:**

In response to the request for the safety update information from ongoing studies (Action letter, Aug 4, 2000, p.5), the Sponsor provided additional information as follows (each point of the letter request is addressed separately and the number of the answer corresponds to that in the request):

1. The Agency letter requested retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission.

The Sponsor included a retabulation of additional data on adverse events from an additional 796 patients from ongoing studies with Definity. The Sponsor found no clinically significant changes in vital signs, oxygen saturation, hematology, serum chemistry, or ECG parameters due to Definity.

2. The Agency letter requested retabulation of drop-outs with new drop-outs identified.

The retabulation of drop-outs was submitted. There were two additional patients who were enrolled and subsequently discontinued. The patients were enrolled and subsequently discontinued prior to trial completion because of AEs (described below) after administration of Definity. One of the patients had a continuous infusion.

*Two additional discontinuations have occurred since the last safety (Patient 020/2/064 and Patient 305/1/108. Narratives for both patients are provided below.*

*Patient 020/2/064 was an 83 year-old white male with a cardiovascular history of multivessel coronary artery disease, ventricular tachycardia, hypertension, and a myocardial infarction in 1980. The patient underwent pharmacologic stress imaging following administration of 0.56 mg/kg of dipyridamole. The patient then received DEFINITY by infusion (1.9 mL DEFINITY in 26 mL of saline) over 5 minutes. The patient experienced bradycardia and hypertension attributable to the dipyridamole injection that resolved within 10 minutes. The patient did not receive additional doses of DEFINITY.*

*Patient 305/1/108 was a 63 year-old white female with a history of hypertension, and left pneumonectomy secondary to cancer. The patient received a single bolus injection of 15  $\mu$ g/kg of DEFINITY. The patient experienced severe back, leg, and chest pain with a concomitant increase in her systolic blood pressure, which completely resolved within 8 minutes without treatment. Due to the AE, the investigator did not continue further dosing.*

3. The Agency letter requested details of any significant changes or findings. The Sponsor did not describe additional changes or findings, stating: *There have been no significant changes or findings with respect to DEFINITY.*
4. The Agency letter requested a summary of worldwide experience on the safety of this drug. The Sponsor stated that *"To date DuPont has not received any new information on the safety of DEFINITY outside DuPont sponsored trials.*
5. The Agency letter requested case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event. The case report forms were provided in the submission.

Narratives for the additional three patients who died (Patients 023/2/204, 305/1/107, and 305/2/203) that were reported in the 2000 annual IND update were provided in this re-submission. Also, 4 patients with a serious adverse drug event were reported.

*Subject 023/2/204 was a 60 year-old white female with a history of aorto-iliac stent graft, right iliac stent, diffuse atherosclerotic disease, borderline hypercholesterolemia, and severe*



*peripheral vascular disease. She also had left leg claudication since May 1999. The subject underwent a visceral angiogram the same day she underwent the unenhanced and DMP 115 contrast-enhanced imaging study. The results of the angiogram confirmed the presence of severe peripheral vascular disease, as well as an aneurysm of the distal aorta extending to the level of the bifurcation, and a critical stenosis of the celiac and SMA. Approximately one day after administration of DMP 115 the subject developed nausea and mild abdominal distention of unspecified duration that the investigator considered as unlikely related to DMP 115. Approximately two days after administration of DMP 115 the subject underwent elective aorto-iliac by-pass surgery. Following surgery the subject became hemodynamically unstable, and developed metabolic acidosis. The subject was intubated, treated with pressors, and sent to the operating room for exploratory surgery. On surgical exploration, cardiac tamponade was discovered and treated. The subject subsequently developed dysrhythmia secondary to the cardiac tamponade and died in the operating room suite following unsuccessful resuscitation. The investigator considered the events to be complications secondary to the surgical procedures, and not related to DMP 115.*

*Subject 305/1/107 was a 58-year-old Filipino male with a history of hepatitis B and hepatitis C, and had multiple hypervascular masses throughout the liver. The subject underwent an unenhanced and DMP 115 contrast-enhanced imaging study. During the DMP 115 contrast-enhanced imaging study the subject received three bolus injections for a total of 2.4 mL of DMP 115. The following day, the subject underwent a liver biopsy procedure. During the procedure, he developed severe coagulopathy and hemorrhaged. The subject died as a result of the severe hemorrhage. The investigator considered the events related to the liver biopsy procedure and unlikely related to DMP 115.*

*Subject 305/2/203 was a 93-year-old white female with a pelvic abscess secondary to a rectal perforation and rectovaginal fistula, with intra-abdominal infection and metastatic disease with metastases to the liver. The subject underwent unenhanced imaging and DMP 115 contrast-enhanced imaging study. During the DMP 115 contrast-enhanced imaging study the subject received five bolus injections for a total of 2.2 mL of DMP 115. Five days after the imaging studies, the subject suffered a cardiac arrest secondary to respiratory failure. She was resuscitated and transferred to the surgical ICU. She subsequently suffered a second cardiac arrest and was not resuscitated in accordance with her family's wishes, and subsequently died. The investigator considered the death a consequence of her underlying condition and not related to DMP 115.*

#### **Serious Adverse Events**

*Patient 022/7/709 was a 71-year-old white male with a cardiovascular history significant for heart murmur, coronary artery disease, and chest pain. The patient underwent rest and stress*

*DEFINITY echocardiography and stress sestamibi imaging in accordance with the protocol. The stress test was stopped because the patient experienced chest pain (treated with 0.4 mg Nitrostat), ST-depression, and fatigue which were all attributed to the exercise stress. The patient's stress test was positive for angina and positive for ischemic ECG changes. The stress echocardiogram was markedly positive for ischemia in the left anterior descending territory, and this ischemia was also apparent on nuclear perfusion imaging. Based on these results, medical therapy for coronary artery disease was initiated for this patient. In accordance with the patient's wishes, he was hospitalized two days later for cardiac catheterization and an angioplasty with stent placement was performed.*

*Patient 023/1/109 was a 69-year-old white female with a cardiovascular history significant for severe vascular disease including aortic stenosis, mesenteric ischemia, and carotid artery repair. The patient was enrolled in the trial one day prior to scheduled aortic-mesenteric by-pass surgery and was administered DEFINITY without incident. The patient developed bradycardia/asystole requiring epinephrine and cardiopulmonary resuscitation for three minutes the evening after aortic-mesenteric by-pass surgery was performed. She recovered without myocardial infarction or other sequelae. The event was considered related to the surgical procedure.*

*Patient 026/2/203 was a 57-year-old white male with a history significant for renal transplant, hypertension, coronary artery disease, chronic obstructive pulmonary disease, and multiple spontaneous pneumothoraxes. The patient underwent a DEFINITY-enhanced ultrasound examination of the kidney without incident. Eight days after the ultrasound examination, the patient was admitted to the hospital for severe bronchitis which was treated and resolved five days later. The bronchitis and subsequent hospitalization was considered related to the patient's underlying disease and not to DEFINITY.*

*Patient 202/1/051 was a 73-year-old white male with a cardiovascular history significant for hypertension, coronary artery by-pass, peripheral vascular disease, and previous myocardial infarction. He was also being treated with digoxin, lopressor, and procainamide. The patient underwent DEFINITY-enhanced echocardiography during dobutamine stress. The patient was hospitalized after he was noted to have developed atrial fibrillation, which was attributed to the dobutamine administration.*

6. The Agency letter requested English translations of foreign labeling. The Sponsor provided a copy of the approved product monograph from the Canadian regulatory authorities and conveyed that a Notice of Compliance was received on December 28, 2000. As far as it can be determined, all the proposed labeling by DuPont was agreed to in Canada..

7. The Agency letter requested information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

The sponsor's analysis concluded that *"AE rates for the patients included in the NDA versus the patients enrolled in clinical trials since the NDA has not revealed any significant changes in the Definity-associated or other new-onset AE profiles submitted with the NDA"*.

#### Pediatric labeling.

In an Action letter of August 4, 2000 the Agency denied a request for waiver of pediatric studies and asked the Sponsor to submit a pediatric development plan with supporting information and documents.

On 22 January 2001, FDA notified the company that DuPont's request for deferral of pediatric studies with Definity was acceptable under 21CFR 314.55(b). However, a partial waiver for pediatric studies in neonates under 21 CFR 314.55(c)(3) and 601.27(c)(3) was not granted. Instead the Agency granted a deferral for the neonatal studies.

In response, the sponsor committed to the post-approval stepwise pediatric study schedule suggested in the 22 January, 2001 letter from the Agency (Introductory letter to this re-submission, p.5, par.5, l.3). A separate submission to that effect was received on April 4, 2001.

#### 4. Efficacy

**(Review limited to wall motion considerations in this regulatory cycle)**

##### Regulatory Overview

The sponsor used the wall motion studies in the original NDA to describe but mainly to support the indication on Left Endocardial Border Delineation. MOR #1 reflected the extent of the studies and their results. The wall motion indication was discussed only briefly since the gain due to the Definity enhancement was considered modest. By averaging the results of unpaired blinded read, omitting all subset analyses, a small statistically significant gain with Definity was observed in 1 (DMP 115 – 006) of 2 trials (Original NDA, Vol.1, p.226 and Vol. 87, p. 175).

The approvable letter of October 8, 1999 suggested that the application lacked sufficient data to validate the use of Definity in the evaluation of wall motion. In response to the Action Letter, a new analysis of earlier data was submitted which showed mainly a decrease in variability among the blinded readers after Definity enhancement. This was likewise considered insufficient, as reflected in MOR #2 (Submission 2/7/00).

In response to the approvable letter of August 4, 2000, the sponsor submitted several (new) analyses of earlier data on assessment of wall motion abnormalities in cardiac patients with Definity contrast-enhanced echocardiography. The data, mostly graphs and tables, are similar for all these submissions (4/7/00, 8/30/00 and 1/30/01) and are the main subject of this efficacy review.

## **MRI as a Comparator**

MRI was used as a comparator. The MRI may be considered at this time the standard of clinical practice, but a systematic assessment of use of MRI for evaluation of wall motion in cardiac patients is not available at this time. As a part of the original NDA, the sponsor submitted a single article (Original NDA, Vol. 77) in support of MRI as a standard for wall motion. That study (Lotan et al., J Am Coll Cardiol 14:1721-1729, 1989) showed only about 66% agreement between the results of wall motion evaluation by MRI and actual presence of a lesion, as determined by coronary angiography.

### **4.1 Concordance Between Baseline Sonocardiography and MRI in Evaluation of Wall Motion**

There are several aspects of the results from the trials (DMP 115 – 006 and – 007) dealing with wall motion evaluation which the Sponsor chose to be highlighted in the third review cycle. Those aspects will be evaluated individually in order of importance, as perceived by this reviewer.

**The data on segmental analysis of wall motion results from DMP 115 – 006 and – 007 were first submitted as a part of Meeting Request of 4/7/00. The same later appeared in the 8/30/00 submission as a pre-meeting package. That material was reviewed in full below. Similar, but materially not different analyses, were found in this re-submission (1/30/00) and were only briefly scrutinized for the sake of brevity of this review. In addition to the data (graphs) which appeared in the two previous submissions, three new ad-hoc analyses were submitted. These do not differentiate between the patients with a normal and abnormal heart. Two of these analyses did not utilize a comparison with MRI results, while another one collapsed the cardiac segments into cardiac regions. Further specifics of all these analyses are given below.**

On the question of concordance between the sonography and MRI, DuPont described its own data. At first (Submission 8/30/00), graphs were presented showing Total Percent Concordance (of Definity-enhanced sonography) with MRI for Wall Motion at Baseline and Following Definity Administration. Segments that were non-evaluable by MRI were excluded from the analysis, and non-evaluable segments by echocardiography were considered to be discordant

(8/30/00 submission, pp. 29 – 36). Thus, the graphs showed the concordance between the two modalities before and after Definity enhancement. Separate points in the graphs represented different cardiac segments. A comparison among the blinded readers was possible, as a separate graph was provided for each of the blinded readers. Each reader determined the evaluability of each segment based on a 3-point scale: 0=nonevaluable, 1=evaluable, and 2=not applicable (i.e. segmental area not captured in the image). The graphs represented an average of the results of the unpaired blinded assessment of each segment (fundamental US after Dose 1). It was noted that a separate graph was also presented for each of the trials in regard to the Institutional Read. The Institutional Read may be biased and will not be discussed further.

A slightly different analysis was offered in this re-submission (1/31/01). Once again, the individual segments within each category were not classified in commonly acceptable designations as non-evaluable, normal, hypokinetic, akinetic and dyskinetic, but rather in clinically inconsequential entities, namely, non-evaluable, normal and abnormal. Segments that were non-evaluable according to the MRI evaluation were excluded (Vol. 6, pp. 00008 - 00012 and 000029 – 000036).

Another analysis was performed on the segments that were non-evaluable by baseline sonography. It also excluded segments that were non-evaluable according to the MRI evaluation. Only the agreement between MRI and contrast sonography was presented. (Vol. 6, pp. 000021 - 000024 and 000059 – 000066). In this regard it is noted that the sponsor inappropriately emphasized an unsubstantiated conclusion, that there was a conversion of non-evaluable segments to evaluable based on the results presented in this analysis and related graphs only (p. 000022, par. 2, l. 1).

For yet another analysis, the earlier “evaluable segments” which totaled 12 were grouped into 5 categories of segments referred to as septum, lateral, inferior, anterior and apical. The segments that were non-evaluable according to the MRI evaluation were excluded (Vol. 6, pp. 000017 - 000020 and 000049 – 000056).

Also, another analysis (#2), while excluding the segments that were non-evaluable according to the MRI evaluation, was concerned only about the perceived improvement in sonography due to the contrast (regardless of the concordance with MRI, or any other comparator) (Vol. 6, pp. 000013 - 000016 and 000039 – 000046).

#### **4.1.1 Concordance Between The Two Modalities in DMP 115 - 007**

As pointed out earlier, the sponsor chose to analyze, in this review cycle, the degree of concordance between sonography, with and without contrast, and MRI. Viewing the graphs from a more clinically relevant (about 75% patients with abnormal heart) trial (DMP 115 – 007;

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS DPM 115 - DEFINITY  
Submission 8/30/00, pp. 34, 35, 36), it is remarkable that for Reader 3, the average concordance between baseline sonocardiography and MRI cardiography for various cardiac segments was about 65%. There was **no change** when comparing the baseline with post DMP 115. Exactly, 76.3% (45/59) patients in that trial had a wall motion abnormality on MRI (original NDA submission, Vol. 83, pp. 349-370). For Reader 4 the overall baseline concordance was even less than for Reader 3, slightly above 50%, with a **very small tendency for "improvement"** with Definity, and only, for certain segments. In two out of twelve segments there was no "improvement", and in three of the twelve there was no change. Only for Reader 5 there was a substantial "improvement" in concordance between US and MRI with the use of Definity after sonography, but this may be due to the sub-par concordance (eight out of 12 segments with 30% or less) for the baseline US. Overall concordance between US and MRI for Reader 3 and Reader 4 was about 60% (p.36) after Definity. **Thus, judging from the results on concordance between MRI cardiography and sonocardiography in this trial, as well as the results on potential improvement after the enhancement, the contributions in the clinic of both sonography as well as Definity are in doubt.**

#### **Blinded Reader 5**

The final reader for this trial, blinded Reader 5 (RML) read both trials (Submission 8/30/00, DMP 115 – 006 and – 007). The baseline sonography read's concordance with MRI for this reader was on the average only 20%, in six out of twelve segments for DMP 115 – 006 (p.32). This was even lower than in DMP 115 – 007 (30%). Although there was a substantial "improvement" after the Definity enhancement, it is noted that the post-Definity results on concordance with MRI for this reader were about 10% better for DMP 115 – 006 than those from DMP 115 – 007. This means, as the data confirm, that Reader 5 who read the results from both trials showed substantially better "improvement" associated with the Definity enhancement, in regard to concordance with MRI, in his read of DMP 115 – 006 than in DMP 115 – 007. Significantly, there were about three times fewer patients with a wall motion abnormality in DMP 115 – 006 (27.7%, 17/62, Vol. 91, pp. 303 -322) than in DMP 115 – 007 (76.3%, 45/59, Vol. 83, pp. 349-370).

#### **4.1.2 Concordance Between the Two Modalities In DMP 115 - 006**

The other two blinded readers from DMP 115 – 006 showed the baseline concordance between sonocardiography and MRI cardiography on the average up to about 65% and noted an "improvement" to about 80 and 90% percent following Definity, that is an increase by 15% - 20% (there was only a negligible increase for 1 of 2 readers in DMP 115 – 007). **To what extent these better results are a real effect of Definity, or are due to the fact, that the patient population in DMP 115 – 006 consisted of a substantial number (72.3%) of patients with no wall motion abnormality, can not be determined from the data in that submission.**

### **Additional Data Comparing the Baseline and Post-Definity Concordance**

The sponsor supplied additional analyses showing some gains in Total Evaluable Segments at Baseline and Following Definity Administration disregarding concordance or discordance with MRI (Submission 8/30/00, pp.19-26). These results may be clinically meaningless, and potentially false. The sponsor's conclusions that there is an "improvement" with Definity would be valid only in case when the baseline reading is truly what it says (highly accurate for the detection of regional ischemia). On the other hand, an uncertain sonography baseline ranging in accuracy from 55% to zero renders the results of that entire analysis meaningless. Consequently, the clinical meaning of the data presented on pages 19 through 26 of the 8/30/00 submission cannot be determined and these results should be considered superfluous in regard to the efficacy evaluation of Definity.

#### **4.2 Direct Comparison of Patients with a Normal and Abnormal heart**

The working hypothesis developed while evaluating the earlier submissions (including the pre-meeting and meeting submissions of 4/7/00, 8/30/00 and 1/30/01) was largely confirmed by additional analyses submitted by the sponsor upon a special request on 3/26/01. For these analyses the sponsor categorized the patients as follows, 1) if any segment was abnormal, the patient was considered to be abnormal; 2) if none of the segments were evaluated as abnormal, but one or more segments were nonevaluable, the patient was considered to be non-evaluable; 3) if all (twelve) segments were normal, the patient was considered to be normal; and 4) patients with non-evaluable segments by MRI were excluded from the analysis, since MRI classification was considered truth (by the sponsor).

##### **4.2.1 Normal Patients in DMP 115 – 006**

In DMP 115 – 006 (March 26, 2001 submission, pp. 1,3,5), the sponsor found 44 patients with **normal** heart (72.19%, 44/61) on MRI and 17 patients with abnormal heart (17/61). Of these 44 patients with normal heart, merely a half was also read correctly as "normal" after the contrast (DEFINITY) sonocardiography by the blinded readers (77%, 39% and 34% by Readers 1, 2 and 5, respectively). The majority of these cases were not read as normal on the **baseline** blinded US read, but rather as "nonevaluable". Therefore, the change in this category was mostly from the "non-evaluable" category to "normal" category. In other words, the positive effect of contrast in patients with normal heart was seen mainly when a patient was nonevaluable on the baseline US. It should not be missed that this applies to patients with the normal heart exclusively. That same conclusion can not be drawn from the entire patient population enrolled in this trial or the study as a whole, as concluded by the sponsor. Other data showing that the results of the current analysis by the sponsor do not support the sponsor's claim are provided immediately below.

#### 4.2.2 Abnormal Patients in DMP 115 – 006

The outcome ~~was~~ different in DMP 115 – 006 (March 26, 2001 submission, pp. 2,4,6) for patients with abnormal heart. In 17 patients with abnormal hearts, 71% of patients were correctly read as abnormal after contrast by all three readers, but a great majority of these were also read abnormal on the baseline US read (65%, 53% and 59% for Readers 1, 2 and 5, respectively). Thus, potential improvement with the contrast was on the average 12% (6%, 18% and 12%, respectively), since all these patients had their **baseline** US scans read as “non-evaluable”. But, as it turns out, this gain could be realized only at a cost in accuracy which was even greater than the potential gain, 14% (12%, 18% and 12%, for Readers 1, 2 and 5, respectively). Thus, no net gain (not in a single patient) was realized in patients with **abnormal** heart in DMP 115 – 006.

#### 4.2.3 Abnormal Patients in DMP 115 – 007

In DMP 115 – 007 (March 26, 2001 submission, pp. 10,12,14) the sponsor found 44 patients with abnormal heart (77.19%, 44/57) on MRI and 13 patients with normal heart (13/57). Of those 44 patients with abnormal heart, roughly a half of the patient studies were read correctly as **abnormal** after DEFINITY by the blinded readers. Exactly, 55% (24/44), 39% (17/44) and 59% (26/44) by Readers 3, 4 and 5, respectively. A large proportion of these cases were also read as abnormal on the baseline blinded US read. Specifically, 88% (21/24), 82% (14/17) and 88% (23/26) by Readers 3, 4 and 5, respectively. From the remaining 7% (3/44) of patients (representing 3 patients with abnormal heart for each reader) that were not read abnormal at the baseline and, thus, represented an apparent improvement, all three were read non-evaluable before the **contrast** by one of the blinded readers, and two were read non-evaluable by the two other readers (the remaining patient was read as “normal”). At the same time, on average 9% patients (11% (5/44), 4% (2/44) and 11% (5/44) by Readers 3, 4 and 5, respectively) with **abnormal** heart on MRI were read incorrectly “normal” after DEFINITY. Thus, once again, no gain due to the use of contrast was realized. Only one patient with abnormal heart who was read “normal” on the baseline read was read correctly as “abnormal” with the help of **contrast** by two out of three blinded readers. However, overall, accuracy did not increase with DEFINITY as compared with the baseline, but decreased.

#### Abnormal Patients in Both Trials

Analyzing the ~~combined~~ results in patients with **abnormal** heart from both trials DMP 115 - 006 and DMP 115 - 007, only 1 patient benefitted by the slimmed margin, 2 out of three readers in one trial (DMP 115 – 007), out of the total of 61 patients with abnormal heart (1.8%, 1/(17+44)), while numerous patients with abnormal heart were read incorrectly as “normal” with DEFINITY



DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS DPM 115 - DEFINITY alone. An average among 5 blinded readers was about 12%, with 12% (2/17); 18% (3/17); 12%, (2/17); 11% (5/44);, 4% (2/44) and 11% (5/44) for Reader 1, 2, 5, 3,4 and 5, in trials DMP 115 – 006 and DMP 115 – 007, respectively. (Please note that Reader 5 read both trials). Thus, according to ~~this~~ analysis, among the patients with an abnormal heart, the benefit was outweighed by cost by the margin of 1:7.

**This does not support the use of DEFINITY as described under this NDA in the diagnosis of wall motion abnormalities in patients with heart disease, since it can not be used with advantage in patients with abnormal heart.**

#### **4.2.4 Normal Patients in DMP 115 – 007**

In 13 patients with normal hearts in DMP 115 – 007 (March 26, 2001 submission, pp. 11,13,15), on the average about 55% of patients were correctly read as “normal” with DEFINITY by all three readers (69%, 62% and 38% for Readers 3, 4 and 5, respectively), but two of the readers read the majority of those as nonevaluable on the baseline US read (46% and 38% for Readers 4 and 5, respectively). The third reader (#3) read about a half of the normal hearts as “abnormal” at baseline. Thus, the potential improvement in the patients with normal heart in DMP 115 -007 was realized only when the hearts were read either “non-evaluable” (2 blinded readers), or incorrectly as “abnormal” (1 blinded reader) at baseline, but not both by the same reader, depending on the reader (exception: 1 patient).

#### **Normal Patients in Both Trials**

Analyzing the combined results in patients with **normal** hearts in both trials DMP 115 - 006 and DMP 115 – 007, it may be concluded that slightly more than 50% were correctly read as such (“normal”) after the use of DEFINITY contrast. This was a noticeable change from the baseline read (without DEFINITY contrast) since most of the cases with normal heart were read as “non-evaluable” at baseline (without DEFINITY) by 3 out of 4 blinded readers. Only one blinded reader (#3) did not read those cases as “non-evaluable” at baseline, but, nevertheless, misread 44% (4/9) his patients normal hearts as “abnormal”, which, likewise, seems an unacceptable cost. Thus, the change of accuracy of the wall motion assessment after administration of DEFINITY to which the sponsor refers as “improvement” is a spurious result of inappropriate analysis of the imaging data. This change is limited only to subjects with normal heart, but it **does not** benefit patients targeted by these studies, namely, those with heart disease.

#### **Normal Patient Images Evaluated by Blinded Reader #5**

It is also noted that one of the blinded readers (#5) **did not read any** of 57 patients with normal heart on MRI **correctly** as “normal” both at baseline and after DEFINITY. This casts doubts on

the ability of this Reader (#5), or if not so, on the methodology itself to have a clinical utility. If a trained reader can not read normal images correctly, then it should not be expected that a reader can read abnormal images correctly using the same methodology (baseline, non-contrast US). In addition, if the result of the baseline read is not correct, as a starting point and a control, then an experimental result to be judged by a comparison with such a control will be in doubt. In fact, only in 34% (15/44) and 39% (5/13) cases in DMP 115 - 006 and DMP 115 - 007, respectively, there was a read "normal" after DEFINITY in patients who had a normal heart on MRI. It may be recalled that the graphical presentation of this reader's (#5) results exhibited the largest positive change ostensibly because of DEFINITY. As documented here, that presumed gain obtained with use of DEFINITY, as reported by Reader #5, is mostly due to misreading of normal hearts as "non-evaluable" or "abnormal" during the baseline read. Reader #5 was also the one who did not observe any gain due to DEFINITY in the entire abnormal-by-MRI heart category. Therefore, **the results of the graphical presentation of data obtained by Reader #5 should be considered spurious and not applicable to patients with heart disease.**

#### **A note on Reader 3 who blindly read the results of DMP 115 - 007**

Reader 3, who blindly read the results of DMP 115 - 007 was specifically mentioned in the first three submissions of this regulatory cycle as follows: 1) "Only Reader 3, who classified nearly every segment as evaluable at baseline and who was previously discussed in CSR DMP 115-007 failed to demonstrate improvement. Also, review of these figures graphically demonstrates that Reader 3 is an outlier" (Submission 4/7/00, p.4, the line before last, and Submission 4/7/00, p.15). 2) "Reader 3, as described in the DMP 115-007 Clinical Study Report, attempted to evaluate every segment whether he could discern wall motion or not. This departure from the way the other readers interpreted the images sets Reader 3 apart as an outlier. Also, review of the figures for Blinded Reader 3, provided in Appendix A, graphically supports the identification of this reader as an outlier." (Submission 1/30/01, p.11, last paragraph). It is noted that the reasons given by the Sponsor can not withstand a rigorous scrutiny.

Within the context of efficacy evaluation of the results of DMP 115 for wall motion, the rejection of results from Reader 3 is inadmissible for the following reasons: 1) The results of Reader 3 for agreement between US and MRI both for baseline as well as after Definity are excellent. Rejection of these results, therefore, would amount to dismissal of the best available data judged by the standard set prospectively. 2) Considering that Reader 5 was unable to read a single patient with a normal heart correctly (as elaborated upon in the previous paragraph) and those results should be interpreted with caution, would leave only the result of Reader 4 to stand. A single reader results should not be considered representative enough to warrant a serious conclusion about a Phase 3 trial results. 3) In addition, a brief look at the graphical presentation of results by Reader 4 shows that this particular reader read some segments better with Definity, but others without. There was only a slight tilt toward the results with Definity, as already

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS DPM 115 - DEFINITY mentioned on page 8, par 2, l.8 of this review. Also, this reader read correctly 39% (17/44) abnormal hearts in patients with an MRI abnormality after DMP, but in 57% patients with abnormal heart at baseline (Submission 3/23/01, p.12). Two patients with abnormal heart who were read correctly at baseline were read incorrectly with Definity, but only one patient read incorrectly improved to correct reading with Definity. Once again, no net gains..

### **4.3 Clinical Impact of Documented Low Accuracy of Sonocardiography with and without DMP 115 in a Patient With Abnormal Heart**

#### **Fundamental Difference Between the Two Trials**

Overall, concordance between the baseline sonography and MRI varies in different cardiac segments and it was on the average between 50% and 65%, except for one reader (Reader #5) where it was about half that (20% to 30%). The more acceptable concordance level improved with Definity only in the trial in which the majority of patients had no wall motion abnormality (DMP 115 – 006).

**Uncertain outcome of a subsequent (experimental) result when the accuracy of initial (baseline) assessment is low.**

Reiterating, with a relatively low concordance between MRI results and the wall motion evaluation by cardiac ultrasound, as documented in this submission, and also the relatively weak relationship between MRI results and the coronary angiography, **the likelihood of accurate assessment of a presence of cardiac lesion (i.e. ischemia) by cardiac baseline sonography is low. Consequently, if it is not certain whether a particular baseline finding reported in this submission is accurate (a lesion present, or absent), any improvement (particularly that disregarding the degree of concordance with MRI) considering the baseline US as a starting point will necessarily be of dubious meaning.** Under those circumstances, essentially all scenarios are possible. An outcome spectrum could range from a full-fledged gain, through minor gain, through no gain, to a meaningless exercise in futility. These all are possible outcomes when the starting point, the baseline ultrasound results, can not be considered accurate, or reliable.

#### **A Hypothetical, “Best Alternative (Most Optimistic)” Scenario**

In a hypothetical scenario only, where the baseline results actually mean what they portend to represent, and the post DMP results as well, a gain due to Definity in trial DMP 115 – 007 was seen only by one (RML, p.26, Submission 8/30/00) of three readers. Another reader (SLS, p.24, Submission 8/30/00) found no difference, since a great majority of all cardiac segments was seen both at baseline and post DMP. The next reader (GPA, p.25 Submission 8/30/00) reported a

small gain. All the readers observed improvement in DMP 115 – 006, but the main gain was observed by all blinded readers in some segments, while it was small in other segments. **If this hypothetical scenario were to be considered seriously, it would be important to note that most of the apparent gain due to Definity was obtained for the cardiac segments with the lowest concordance between MRI and baseline US.**

### **Recent submissions on efficacy**

Two most recent submissions (Submissions 4/16/01 and 6/21/01) were subsequently briefly reviewed based on their merit, but were found not contributory. The content of these submissions does not alter conclusions of this review.

In the first of these submissions, conversion of adjacent non-evaluable segments (#1) in a patient determined by individual readers was analyzed according to the results of MRI (normal, abnormal, intermediate) and trial (DMP 115 – 006 or DMP 115 - 007). This was a partial analysis which did not consider overall impact of the use of the contrast agent in a patient population, but only considered those patients who benefitted. Therefore, it would be inappropriate to consider this analysis as conclusive, or to be viewed in isolation.

This submission also states that (#2) the left endocardial border delineation was evaluated based on observation of endocardial edges and myocardial thickening. Furthermore, this submission also contains a copy of Canadian Product Monograph for this product. Since it is not known what data was submitted for review to Canadian authorities the numbers shown can not be subjected a reasonable scrutiny. From reading the Monograph, one can reasonably conclude that on important points it reflects closely the company's viewpoint.

The other submission (6/21/01) focused on agreement between post-Definity contrast US and MRI in converted adjacent non-evaluable segments at baseline (Table 1). Again, it considered only the patients who benefitted. This analysis should be viewed as informative, not conclusive, since a total conclusion can not be drawn. It disregarded the difference in the proportion of patients with normal and abnormal hearts in the two trials by pooling the patients for analysis. Except for Reader 3, who consistently read all images with high accuracy, similarly for both with Definity and without, the agreement of other two readers for DMP 115 – 007 is about 50%. The average of all readers in DMP 115 – 006 is also about 50 %. Although the difference in patient population between the two trials seems somewhat less important when only two or more non-evaluable segments at baseline are considered (Table 2), this may be a computational flaw, since the difference between DMP 115 – 006 and – 007 in favor of the former shows again when the analysis is done by region.

The concordance between the results of post-contrast (Definity) US and MRI for at least two baseline non-evaluable segments was the subject of another assessment in one of the subsequent submissions (Submission 6/29/01). Overall, this concordance is slightly 50% (Table 1) and the number s of patients are small when subclassified into "normal" and "abnormal" groups. Although for 2 readers the average of "normal" and "abnormal reads is around 70%, the clinical meaning and practical implication is not clear. In this patient classification, the data appear to favor the patients with abnormal for better agreement MRI. However, a physician in a clinic will never know in advance if the patient has abnormal heart, or not. Secondly, even if the concordance between the Definity US and MRI is 0.7, it was pointed out earlier in my reviews that the agreement between the wall motion assessment by MRI and coronary angiography in the diagnosis of coronary artery disease is 0.62 and 0.66. Therefore, the Definity US may diagnose the coronary artery disease in adjacent non-evaluable segments with less then 50% accuracy. Similar conclusions can be drawn for "at least two converted segments" (Table 2). Grouping patients by the number of converted non-evaluable segments in Tables 3-5 (2, 3-5, 6 and more) further reduces the number of patients per group and increase variability among the blinded readers. Two of the readers show consistently better results than others, but no conclusive evaluation is possible from the subset analysis because of small numbers.

On June 27, 2001 the sponsor submitted a revised table on adverse events to include the number of patients with ADE categorized by organ system.

On July 9, 2001 a response was received to a request for a statement on financial disclosure. Since the studies were completed before 1999 the financial information statement is not a requirement. The sponsor noted that in this letter.

Also on July 9, 2001 as a separate submission, tables were submitted showing mechanical index (MI) used in the imaging studies in individual patients. It ranged from 0.3 to 1.6 (mean =0.8) in the four clinical trials used for efficacy assessment. In a related submission (7/12/01) the sponsor showed that for 83% patients in the Phase 3 efficacy studies the MI was 0.8 or less. The submission of July 11, 2001 contained descriptive statistics for the mechanical index used in pivotal Phase 3 trials. It also revealed that the MI used for harmonic imaging was slightly higher (mean = 0.9).

In the July 10, 2001 submission the company committed to performing a post approval pre-clinical study to determine the fate of the activated microspheres, characterizing the length of microsphere ~~persistence~~ and the potential for microsphere gas exchange.

In another submission (7/12/01) the company committed to complete pre-clinical studies of the effects of mechanical ventilation on the microbubble characteristics and toxicity, similar studies

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS DPM 115 - DEFINITY  
in adults, and to submit a Proposed Pediatric Study Request (PPRS) within 120 days of the  
action letter.

#### **4.4 Conclusion:**

The new analyses of earlier efficacy results on wall motion (DMP 115 – 006 and - 007) reveal that the data may be best explained by a different concordance (between sonocardiography, with or without Definity enhancement, and MRI) in patients with normal and abnormal heart. Current analyses obtained by a special request from the sponsor confirm that in patients with heart disease (abnormal heart) no gain resulted from sonocardiography using the DEFINITY contrast. In subjects with normal heart on MRI an “improvement” was seen which occurred mainly when normal hearts were mistakenly read as abnormal, or non-evaluable on baseline US read.

#### **Recommendation:**

The results submitted do not support a wall motion indication. Data are needed to demonstrate the ability of Definity-enhanced US to contribute to the diagnosis of heart disease. One of the options is to correlate the results of Definity with coronary angiography as the standard of truth for CAD.

#### **4.5 Trend assessment:**

According to the tables provided by the sponsor (23-Mar-01 submission), all the blinded readers correctly found an abnormal heart more frequently without Definity than with Definity. Therefore, it appears that no positive trend manifested in the wall motion evaluation in any of the two trials in the category of patients with heart disease.

The same blinded readers correctly found a normal heart about 3 times as frequently with Definity than without. However, these blinded readers diagnosed a normal heart with the help of Definity on the average only in 55% - 60% cases. In the trial with more normals (DMP 115 – 006) this average was close to 50%. Thus, although Definity helped in the correct diagnosis of normal heart as compared to a non-contrast US, its overall performance was only slightly better than tossing a coin.

At this time it appears that better contrast due to Definity, as described by the sponsor, does not have a functional correlate. - At least, not with the wall motion, as apparent from the data analyses provided by the sponsor so far.

The sponsor should be encouraged to attempt to respond to the Agency suggestion to try to explain the inconsistency in results between the early trials (DMP 115 – 006 and –007) as stated in the Action letter of August 4, 2000 and perform a complete statistical analysis (including subset analyses) to look for other potential trends.

## DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS DPM 115 - DEFINITY

If not successful, further trials would be needed to obtain data demonstrating the ability of Definity-enhanced US to contribute to the diagnosis of heart disease. One of the most apparent options is to correlate the results of Definity with coronary angiography as the standard of truth for CAD.

Other trials could explore the potential seen above with the normals by studying subgroups of normal subjects.

**5. Summation:**

The Sponsor provided a number of satisfactory answers to the Agency suggestions, but the efficacy question regarding the functional justification for the proposed indication was not addressed in an acceptable way.

**Regulatory:****Efficacy:**

The re-submission did not describe data to validate the use of DEFINITY in the evaluation of cardiac wall motion. No additional studies were provided. The indication for cardiac wall motion is, therefore, not approvable.

**Safety:**

1. The impact of activated microspheres on safety was tested in animal studies, but the results did not support a conclusion that the drug is unequivocally safe.

**Safety Update:**

The Sponsor requested a waiver from the pediatric labeling for DEFINITY under 21 CFR 314.55(b) and supplied the retabulation of safety data as outlined in the Action Letter of Aug 4, 2000. The safety update is satisfactory and the Sponsor committed to perform pediatric development studies in a stepwise manner as suggested by the Agency. A separate submission to that effect was received on April 3, 2001.

**Scientific:**

1. The data on the safety profile did not change appreciably since the original submission. However, the evaluation of the safety profile continues unresolved because of the lack of clinical data, such as EKG, obtained in a timely manner.
2. The data and analyses provided in this re-submission contain no additional evidence to alter the original FDA efficacy assessment.

**6. Recommendation: APPROVABLE.**

CC: NDA Archive

HFD-160/ Division File

HFD-160/ T.Nguyen/Zolman

**ISI**  
Medical Officer

Redacted 40 18

pages of trade

secret and/or

confidential

commercial

information



NDA# 21-064

M.O. Review # 2

Date of letter: 2/7/00

Date FDA received: 2/7/00

Date reviewer received: 2/8/00

Date review completed: 4/18/00

**1. General Information**

**Drug name:** DMP 115  
**Generic name:** Perflutren  
**Proposed trade name:** DEFINITY  
**Chemical name:** Phospholipid liposomes with perfluoropropane in saline  
**Status:** Response to Action Letter of October 8, 1999  
**Sponsor:** DuPont Pharmaceuticals  
331 Treble Cove Road  
North Billerica MA 01862

**Reviewers:** Statistics:  
Pharmacology/ Toxicology:  
Biopharm:  
Chemistry:

**Note:** All the statements made by Sponsor in the NDA submission, which appear in this review, are in *italics*. These were transferred from the submission ad verbatim.

**Pharmacologic Category:** Sonographic contrast agent  
**Proposed Indication(s):** *for contrast-enhanced ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders) and function (regional wall motion)*

**Submissions for this Review**

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	CONTENT
Amendment (AZ)	7-Feb-00	8-Feb-00	8-Feb-00	Re-submission
Amendment (BZ)	13-Mar-00	14-Mar-00	14-Mar-00	Response to request for inf.

**Dosage Form(s) and  
Route(s) of Administration,  
Directions for Use:**

*... a single dose 10 uL/kg by slow I.V. bolus injection over 30-60 seconds, followed by a 10 ml-saline flush. A second 10 ul/kg dose may be administered to prolong optimal imaging. May also be administered via an I.V. infusion of 1.3 ml added to 50 ml of preservative free saline. The rate of infusion is suggested to be initiated at 4 ml/minute, but should be titrated as necessary to achieve optimal image enhancement.*

**Related Approved Drugs:** Albunex, Optison  
**Related Reviews:** Statistical Review, Biopharm Review, Chemistry Review, Pharmacology/Toxicology Review

**2. Table of Contents**

1. General Information .....	1
2. Table of Contents .....	2
3. Material Reviewed .....	2
3.1 Regulatory Update.....	2
3.2 Safety.....	8
3.3 Efficacy.....	17
4.1 Summation.....	19
5. Recommendation.....	20

**3. Material Reviewed**

This re-submission is comprised of a total of 16 volumes of roughly 400 pages each. Clinical data appeared in volumes 1 and 8 - 13, a total of 7 volumes. The re-submission was reviewed in full.

The re-submission was submitted as a response to the action letter of October 8, 1999. The Sponsor's answers to individual items contained in the action letter are addressed below in sequential manner in the same order as they appeared in the action letter. Essence of each FDA request ~~precedes~~ the answers. Detailed reasoning and data analyses can be found later in this review.

**3.1 Regulatory Update**

**3.1.1 A. Efficacy:**

1. The Agency letter requested data to validate the use of DEFINITY in the evaluation of cardiac wall motion.

No new primary data was provided to validate the use of DEFINITY in the evaluation of cardiac wall motion. The Sponsor chose to deal with the request by offering an unusual, new analysis of imaging results, which lacks validation at this time. Please, refer to page 17, Section 3.3.1 for details. Unsatisfactory response.

2.

**B. Safety:**

1. The Agency letter noted that the activated microbubble upper limits of the particle size distribution lack sufficient manufacturing control to ensure safety of the administered product.

The Sponsor complied with many of the Agency's specific suggestions regarding the limits of particle size, but the main question, how to assure that the particles larger than 10 um are excluded, remains to be resolved.

- a. The Agency letter asked to adjust the manufacturing controls to ensure that particles are less than 10 um in diameter.

The Sponsor did not agree to . . . immediately prior to the drug injection or infusion. Please refer also to the chemistry review. Unsatisfactory response.

b. The Agency letter asked for completion of a special pharmacology study to evaluate the risk of use of DEFINITY in patients with a chronically compromised pulmonary vasculature disease model.

The Sponsor attempted, but did not complete satisfactorily a special pharmacology safety study to evaluate the risk of use of DEFINITY in patients with a chronically compromised pulmonary vasculature. This issue was discussed with the reviewing pharmacologist. Please refer to pharmacology/toxicology review. Unsatisfactory response.

c. The Agency letter suggested an additional bridging study to assess the suggested manufacturing approach and the results of the above special safety study.

No bridging study is planned at this time. Unsatisfactory response.

2. The Agency letter asked for sufficient data to characterize the risk of arrhythmias. The Sponsor provided some data to evaluate the risk of arrhythmias.

a. The Agency letter suggested a safety pharmacology cardiovascular study using a wide range of human dose multiples based upon body surface area.

The safety pharmacology cardiovascular study was satisfactorily completed, although "It would have been helpful to use a dose of Definity that would have elicited adverse cardiovascular event...." (Pharm/Tox review, p.11, par. 3, l.4). The study performed by the Sponsor is considered sufficient. This issue was also discussed with the reviewing pharmacologist. Please refer to pharmacology/toxicology review. Satisfactory response.

b. The Agency proposed an in vivo evaluation of potential for clumping, aggregation or coalescence in systemic circulation.

No satisfactory in vivo evaluation of potential for clumping, aggregation or coalescence in systemic circulation was performed. The preclinical study performed mouse cremaster muscle where the median arteriole diameter is rather large, 22  $\mu$ m. In addition, the size and concentration distribution of the DEFINITY formula used was not described. This issue was likewise discussed with the reviewing pharmacologist. Please refer to pharmacology/toxicology review. Unsatisfactory response.

c. The Agency letter requested data to support completion of evaluation of the risk of QTc prolongation, rhythm disturbances or other myocardial conduction abnormalities.

The Sponsor provided some information on the rhythm and other conduction abnormalities that were associated in the patients who had prolongation of the QTc interval greater than 0.03 units. About 10% of patients administered DEFINITY by bolus or continuous infusion had drug associated ECG abnormalities in conjunction with a

QTc prolongation. For details please refer to Section 3.2.1, p. 8 of this review.  
Satisfactory response.

d. The Agency letter requested bridging studies, if needed, depending on the outcome of the data above in this section.

No additional clinical bridging study was accepted or attempted reasoning that DuPont firmly believes that DEFINITY is safe. Sponsor cited a recently completed preclinical study in monkeys. Unsatisfactory response.

3. The Agency letter requested data to complete the adverse event risk assessment. Specific requests were made for a table that separates the events of each placebo and a table that compares each dose given by bolus and by infusion.

Separate tables for ADEs were provided for two treatments considered to be placebos by the Sponsor (Vol. 9, pp. 3 – 13) and for different doses administered by bolus and by infusion Vol. 9, pp. 14 – 362). The number of patients who received vehicle-placebo was exceedingly small (14 subjects versus 229 subjects who received the drug). Saline was administered to 48 patients, but in this trial it does not conform to the placebo definition since it is visually easily distinguishable from the drug, or vehicle. The drug administration by infusion decreased occurrence of ADEs by about 60% for most of the parameters, except for QTc prolongation and ECG changes. No other variables, including different doses, were found to have significant effects on ADEs. For details, please refer to Section 3.2.2, page 14 of this review. Satisfactory response.

4. The Agency letter requested data to characterize the safety profile of the infusion of 1.3 ml DEFINITY in 50 ml saline in echocardiography.

ADE tables were provided on additional patients studied by continuous infusion. Forty six ADEs were reported on a total of 390 patients (March 13, 2000 submission, pp. 60 – 80). While the number of ADEs is relatively low, the decrease when compared with the bolus administration appears similar across all the safety parameters with the exception of QTc prolongation and related ECG changes. A more conclusive statement about the safety of infusion must await further studies. Please refer also to p. 15 of this review. Satisfactory response.

5. The Agency requested additional data on reproductive toxicology performed with the final to-be-marketed formulation.

The Sponsor provided adequate data on reproductive toxicology. This issue was discussed with the reviewing pharmacologist. Satisfactory response.

In regard to ~~special~~ training, the sponsor committed to provide such training and also appropriate manuals and leaflets advising about proper DEFINITY use. Please refer also to chemistry review. Satisfactory response.

**Safety Update:**

In response to the request for the safety update information from ongoing studies (Action letter, Oct 8, 1999, p. 28) the Sponsor provided additional information as follows (each point of the letter request is addressed separately and the number of the answer corresponds to that in the request):

1. The Agency letter requested retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission.  
The Sponsor provided retabulation of additional data on adverse events, from the studies incomplete at the time of original NDA submission, which include patients, most of them receiving bolus injection. For the bolus administration the retabulation was deemed superfluous because "The incidence rates would not be expected to change considering that only 12 additional patients received DEFINITY as a bolus injection" (Vol. 1, p.208, par. 5, l.3). A direct comparison between the bolus administration and infusion was presented in a tabular form as requested. A narrative refers to 390 patients who received the infusion (Vol. 1, p. 209, par. 2, l.1), but only the results on 188 were tabulated (for example Vol. 9, p.233, Table 17 B, last column). An analysis of the comparison by this reviewer is described in Section 3.2.2 on page 14 below. Satisfactory response.
2. The Agency letter requested retabulation of drop-outs with new drop-outs identified.  
The retabulation of drop-outs was submitted. There was one additional patient which was enrolled and subsequently discontinued. That patient was enrolled and subsequently discontinued prior to trial completion, but received all DEFINITY doses and completed echocardiographic imaging. Satisfactory response.

*The patient was a 60-year old white male who entered the trial with a medical history of MI, and a percutaneous transluminal angioplasty (PTCA) with stent placement in 1998. Two minutes following the second DEFINITY infusion and 5 min post-treadmill exercise, an ECG revealed ST segment depression in V3-V6. At 6 minutes post exercise, the patient collapsed and was in ventricular tachycardia (VT). Cardiopulmonary resuscitation was initiated along with 100% O<sub>2</sub>. The patient was cardioverted, and was then in asystole. Intravenous access was lost, and CPR was re-initiated. The cardiac rhythm returned with sinus bradycardia followed by sinus tachycardia. No medication was given. The ECG returned to baseline. The patient was conscious and oriented. Following this event, the patient had a cardiac cathetrization in which he was noted to have 100% diagonal lesion, an 85% right coronary artery (RCA) lesion and a 100% right posterior left ventricular lesion. Subsequently, the patient underwent a revascularization procedure of the RCA with good results. Since the VT/ventricular fibrillation (VF) arrest, a MI has been ruled out. The investigator considers the VF arrest to be related to ischemia following exercise and considers the events to be unrelated to either the DEFINITY and Sestamibi administration (administered 10 minutes*

*after the first -baseline - DEFINITY infusion and treadmill exercise). For more details please refer to Re-submission, Vol. 1, p. 213, par. 3. The explanation by the sponsor is dubious since a 100% coronary artery lesion is usually associated with myocardial infarction. Also, it was not explained what the diagonal lesion is.*

3. The Agency letter requested details of any significant changes or findings.  
The Sponsor did not describe additional changes or findings, stating: *There have been no significant changes or findings with respect to DEFINITY.* Satisfactory response.
4. The Agency letter requested summary of worldwide experience on the safety of this drug.  
The Sponsor did not address specifically the question of worldwide experience. The Sponsor stated that *DuPont has recently acquired rights to ImaRx's technology, including responsibilities as licensor to . . . which has rights to develop this imaging agent in . . . and other . . . countries. DuPont expects to be meeting with . . . to acquire access to their clinical experience and safety database.* Satisfactory response.
5. The Agency letter requested case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.  
Case report forms for each patient who died during a clinical study or did not complete a study because of an adverse event were provided in the original submission. One serious ADE summary was provided (described under # 2 above). Satisfactory response.
6. The Agency letter requested English translations of foreign labeling.  
English translations of approved foreign labeling not previously submitted were not attached because *"DuPont has no new approved foreign labeling."* Satisfactory response.
7. The Agency letter requested information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.  
The information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events was not addressed specifically. The Sponsor stated: *Comparison of incidence rates for the patients included in the NDA versus the patients enrolled in clinical trials since the NDA has not revealed any significant changes in the DEFINITY-associated or other new-onset AE profiles submitted with the NDA.* Satisfactory response.

~~Pediatric labeling.~~

The Agency asked the Sponsor to submit a pediatric development plan or request a waiver with supporting information and documents.

The Sponsor argued that the use of contrast in pediatric cardiac studies is not warranted due to the limited chest circumference and distance of the heart to the chest wall in children. In addition, transducers with higher frequency may be used (because of limited penetration).

is reduced in pediatric population compared to an aged population. Also, a point was made that other modalities such as MRI and CT can be used in children with advantage.

Although both these points may be true, they cannot be considered to be significant obstacles to potential future use of contrast ultrasonography, particularly if proven to be effective. Thus, although pediatric use of sonographic contrast may be somewhat limited in certain situations, this should not stop its development in pediatric population. The Sponsor requested a waiver from the pediatric development of DEFINITY as defined under 63 FR 66632A. Satisfactory response.

### **3.2.1 Safety: Rhythm and conduction abnormalities in patients with QTc prolongation**

#### **Approvable letter**

The approvable letter of October 8, 1999 stated under Section I. Clinical and Statistical, Part B, Safety 2 that "The application lacks sufficient data to characterize the risk of arrhythmias." As for the specific deficiencies, it requested under Safety 2 (c) : "The provision of information on the rhythm or other conduction abnormalities that were associated in the patients who had prolongation of QTc interval greater than 0.03 units."

#### **Re-submission**

Of the total of 70 patients (Vol. 8, p. 32, Table 1) counted (with the prolongation of QTc by more than 0.030 units) only 5 were analyzed in the re-submission. For the rest of the patients only a line listing was provided (Vol. 8, p.126, Table 5.1). The line listing was the basis for an analysis described later in this review.

#### **Request for additional information**

As the data in the re-submission was considered insufficient, another specific request for information was made by a fax on March 6, 2000 which read as follows: "In response to the approvable letter of October 8, 1999, Section I, Part B, Safety(2) (c only a list of 5 patients with QTc increase greater than 0.03 unit was supplied. However, a line listing provided (Vol. 8, p.126, Table 5.1) also showed numerous other patients eligible for analysis of rhythm and conduction abnormalities. Please provide a complete analysis and summary of what the abnormalities were,



relationship to the increases in QTc, and whether and how the rhythm and conduction abnormalities resolved.”

### **Time points in ECG study**

As stated in the original NDA review, ECGs were first obtained 30 min following the imaging procedure. That means 90 min after the start of injection or infusion since each of 2 imagings lasted about 30 min.

### **Limited ECG data**

As shown in a response to the March 6, 2000 fax received on March 13, 2000 (Table 5.1A, pp. 015 – 032, also Re-submission February 8, 2000, Vol. 8, Table 5.1A, pp. 126 – 157), in some cardiac patients (DMP 115 –004, –005 and 017) a baseline ECG was obtained and then four other ECGs up to 72 hrs post-treatment. The rate of QTc prolongations observed, as reported by the Sponsor (Re-submission, Vol. 8, p.125, Table 1) was 18.3% (31/169) for the combined DMP 115-004 & DMP 115-005 trials and 18.8% (12/64) for DMP 115-017. In the remaining trials, DMP 115 -006, -007 and DMP - 009, -010, an ECG was obtained only once after the drug injection (either at 30 min post-injection, or at 24 hrs post-injection) which decreased (11.9% and 5.7%, respectively) the rate of detection of prolonged QTc intervals. Because of paucity of measurements these cannot be considered to be reliable estimates of true incidence.

### **Missing data in ECG analysis**

However, the numbers reported in Table 1 (Vol. 8, p.125) are erroneous. First of all, they do not agree when compared with the number of patients reported in the line listings (Table 5.1A, pp. 126 – 157). For DMP 115 – 004 and - 005, 14 and 23 patients, respectively, are line listed with QTc increases for the total of 37. This would give an incidence of QTc increases 21.9% (37/169) instead of 18.8% (31/169) reported by the Sponsor. Secondly, the number of patients reported with a QTc prolongation do not include those with such an increase observed during the entire interval when all the measurements were taken, but considering only those with the first measurement as a starting point. There were, at least, 14 additional such patients. Since those patients were not line listed, they also could not be counted if and when they had an ECG change. In addition, there are some (12 additional patients) primary EKG data missing. All the QTc data could not be calculated also for those. These patients were erroneously included by the Sponsor into the denominator (169). That would bring the percentage of patients with a more than 0.030 unit prolongation to 32.5% (51/157) which is about twice the percentage reported by the Sponsor.

For DMP 115 – 017, the true incidence is 20% (13/64) instead of 18.8% (12/64) as reported by the Sponsor.

#### **ECG changes in DMP 115 - 004**

In DMP 115 – 004, as per the line listing of patients (Submission March 13, 2000, Table 5.1A, pp. 015 – 019, also Re-submission February 8, 2000, Vol. 8, Table 5.1A, pp. 126 -130) with an increase in QTc >0.030 unit, 50%(7/14) had a related ECG change (3 PVC, IVCD, RBBB, PAC-LVH, Poor R Wave progression). There was no apparent dose response relationship. Thus, the overall incidence of a drug related ECG change in this patient population was just over 10% (7/69). In addition, there are some missing EKG data on 3 patients and 5 patients had the QTc increase sometime during the follow-up, but are not counted as such (without an ECG assessment). In regard to the design of this trial, it may be recalled that 12-lead ECG monitoring was done at the baseline, again within 30 minutes after the second imaging, and continued after 24 hours, 48 hours and 72 hours. The patients were injected by bolus twice with 5 uL/kg or 10 ul/kg DEFINITY.

#### **Duration of ECG changes**

The ECG changes after the drug were usually present for more than 24 hours and continued when the ECG reporting stopped (as per line listings).

#### **Nature of ECG changes**

Although the rate in patients who received “placebo” was similar in this trial (please, refer to Appendix A at the end of this review) those changes were not of comparable severity (PVC, LAE, NT, NSTT, LT, SBRAD, LVH, SAR) with a possible exception of PVC.

#### **ECG changes in DMP 115 - 005**

In DMP 115 – 005, as per the line listing of patients (Submission March 13, 2000, Table 5.1A, pp. 020 – 025, also Re-submission February 8, 2000, Vol. 8, Table 5.1A pp. 136 -141) with an increase in QTc >0.030 unit, 29%(7/23), had related ECG changes (IRBBB-LAE-RAE-REPOL, ST and T wave c/ ischemia, AFIB-ST depression c/ anterior ischemia, RAD,-NST, PVC- anterolateral ischemia, NSTT-LT-SAR-prolonged QT interval). The ECG line listings were not provided on 9 patients, who had a QTc prolongation more than 0.030 unit some time during the follow-up, but not when compared with the starting point. In addition, there was some EKG data missing on 9 patients and adequate QTc data could not be obtained. However, as already mentioned, all these patients were counted and increased the denominator when the Sponsor

calculated the incidence of a QTc prolongation. Subsequently, that data does not appear in the line listing and the ECG assessment.

#### **Outlier data from site 4**

It is apparent (from the data which was provided) that more than a half of all cases with the QTc prolongation (56.5%, 13/23) were observed in a single trial (Site 4) where the occurrence of a more than 0.030 unit prolongation was 65% (13/20). A disproportionately large number of these QTc prolongations appeared late after DEFINITY injection. Only 1 of those patients had a related change in ECG. Out of 20 patients who received the drug, 16 were 42 years old or younger, which is not typical of a cardiac population for which this drug is intended. For all these reasons, this trial of 20 patients who received the drug and 5 patients who received placebo is considered an outlier for the purpose of this analysis and will not be considered further.

#### **Remaining ECG data for DMP 115 - 005**

Among the patients (10) from the rest of the investigators in this trial (DMP 115-005), with QTc changes reported by the sponsor, there were more patients (6/40) who received 5 ul/kg and had the QTc change as compared to those who received 10 ul/Kg (4/40). The same number of patients (40) received each dose. From the first group (5 ul/Kg) a larger proportion (4/6, 66%) had a drug related ECG change as compared to the second group (10 ul/Kg) where it was (1/4, 25%). Therefore, there was no apparent dose response relationship regarding the ECG change observed among these cardiac patients (DMP 115 -005). The overall rate for ECG change among patients in this section of the trial was 6.25% (5/80). This incidence rate, which is somewhat lower than in DNP 115-004, may be due to a large number of patients with missing primary ECG data (9/80) and/or the omitted QTc line listing (9/80). Considering patients with full data, the rate of ECG change in this trial is 8% (5/62). The trial had a similar design as DMP 115 - 004.

#### **"Placebo" comparison**

Among the patients who received "placebo" (saline), 5 (19) had a QTc prolongation (Appendix A) and from those only 1 had an ECG related change for the resulting rate 1 of 5 (20%) and overall rate 5% (1/19). The latter may be considered an occurrence by chance only in patients with Class 1 and Class 2 cardiac disease, but not in an acute distress, in this trial.

#### **Duration of ECG changes**

The ECG changes after the drug were usually observed for more than 24 hours and not monitored to resolution.

#### **ECG changes in DMP 115 - 017**

In a line listing submitted (Submission March 13, 2000, Table 5.1A, pp. 030 – 032, also Re-submission February 8, 2000, Vol. 8, Table 5.1A pp. 155-157), 4 out of 13 patients, had a pacemaker. One of these four patients showed ECG abnormalities following the drug administration. Out of the remaining 9 patients with QTc changes reported by the sponsor, 4 (44%) showed ECG abnormalities after the drug exposure (bolus or infusion). These abnormalities were usually recorded after the first imaging session as well as before and during the second imaging session (second dose), including an ECG obtained before the second imaging. There was a 24 – 72 hour interval between the imaging sessions so that it may be assumed that the abnormalities lasted at least for that interval. Three out of those four patients received the DEFINITY infusion on the first day. Therefore, at least in this trial with cardiac patients, DEFINITY infusion was no better than the bolus injection.

The overall incidence of a drug related ECG change in this trial, not considering the patients with a pacemaker, was 6.6% (4/64). It was almost 10% (3/32) among the patients who received the infusion first. It was 25% (1/4) in patients with a pacemaker. Patients with pacemaker cannot be considered for overall analysis as the effect of the pacemaker may be confounded with that of the drug.

#### **ECG changes in DMP 115 - 006, -007, -009 and -010**

As mentioned before, in the remaining trials DMP 115 -006, -007 and DMP - 009, -010, an ECG was obtained at baseline and only once after the drug injection. In DMP 115 –006 and –007 ECG was obtained at 30 min after second-imaging (at least 1 hr after the first injection) and in DMP 115 –009 and -010 at 24 hrs post-injection. (Submission March 13, 2000, Table 5.1A, pp. 028 – 029, also Re-submission February 8, 2000, Vol. 8, Table 5.1A pp. 146 -154). This decreased (11.9% and 5.7%, respectively) the rate of detection of prolonged QTc intervals. Because of paucity of measurements these ought not to be considered reliable estimates of true incidence of a QTc prolongation and the associated ECG changes. The latter is mentioned here only for completeness.

Only two ECG changes stand out in the first two trials (DMP 115 – 006 and –007). There was a new reading of anterior myocardial infarction (AMI) in a 75-year old male (115-006/1/26) with atrial fibrillation (AFIB), nonspecific ST abnormality (NSTT) and right axis deviation (RAD). There was also a new reading of premature ventricular contractions (PVC) in a 65 year old male (115-007/1/6) with earlier ECG evidence of infarct. Both of these were seen at 30 minutes post-imaging, and there is no record of farther follow-up.

In the other two trials, only one finding stands out. A case of premature ventricular contractions (PVC) associated with sinus tachycardia (STACH) in a 51-year old male (115-010/1/210/K/2) without any abnormality on the baseline ECG. This ECG was obtained at 24 hours post imaging.

#### **Sponsor's analysis of ECG data**

In the response to a specific request for evaluation of ECG data and evaluation (Submission March 13, 2000, unnumbered pages), the Sponsor described ECG data from 3 patients with QTc prolongation and atrial fibrillation and one case of sinus bradycardia. Patients with PVC or other changes were mentioned in passing emphasizing that no therapy was needed. No details on 9 patients with PVCs and the patients with other ECG changes were provided. The treatment of this subject in the re-submission was similar.

Numerous instances of data omitted from the analysis were noted earlier. The Sponsor also described some of the data on ECG inaccurately. For example, in trial DMP 115 – 017, all patients received both treatments (bolus and continuous infusion) in a cross-over design (50% of them in a reverse sequence in randomized fashion).

These patients (64) received two injections, 10 ul/kg DMP 115 each by bolus, and its equivalent, 1.3 mL of DMP 115 diluted in 50 mL of preservative-free saline. Therefore, it is not appropriate to refer to this trial as if each patient (64) received each administration separately (Submission March 13, 2000, Vol. 8, p.125, Table 1). Similarly, it is not appropriate (Re-submission, Table 1, Section 1, non-numbered pages) to consider the dose to be 40 ul/kg (instead of 20 ul/Kg) and compare it to 5ul/Kg (10ul/Kg) in other trials such as DMP 115–004, -005 (DMP 115 – 006, -007). The latter doses were used as two bolus injections for the total 10 ul/kg and 20 ul/kg, respectively.

The Sponsor found no evidence of a dose response relationship between DEFINITY and ADEs with increasing dose.

#### **Conclusion:**

1. Data provided by the Sponsor to analyze the ECG changes in patients with prolonged QTc interval after DEFINITY injection or continuous infusion is incomplete in several respects. Mainly, the record was not provided in this submission for at least 15 patients (out of the potential total 52) treated with DMP 115 who had a QTc prolongation within 72 hrs post-injection in DMP 115 –004 and –005. This represents 33.3% (7/21) of eligible patients in DMP 115 – 004 and 44.4% (8/18) of eligible patients in DMP 115-005. **Thus, more than a third of pivotal data was not evaluated by the Sponsor.**

2. The data analysis of the remaining ECG changes in patients with a QTc prolongation is erroneous and might have missed the true incidence of QTc prolongations. Although the true incidence is likely twice the number provided, the Sponsor concluded that 18.3% of the patients in DMP 115-004 and -005 had a QTc prolongation.
3. Other ECG changes may be related to DEFINITY. About 10% patients experienced these in three trials where sufficient database is available and where an ECG was obtained more than once after DEFINITY administration.
4. A variety of ECG changes were observed. PVC occurred in 9 cases. As most of the other new ECG findings in the trials with DEFINITY, these were found repeatedly in the same patient.
5. ECG changes observed after DEFINITY administration were lasting more than 24 hrs.
6. No dose-response relationship was found between DEFINITY (administered by bolus or by infusion) and the occurrence of QTc lengthening or ECG changes in patients with such a lengthening.
7. There is no evidence in this data that the administration of DEFINITY by infusion confers any benefit compared to bolus injection (in respect to the occurrence of QTc and/or related ECG changes).
8. The lack of evidence for dose response relationship or the effect of infusion does not exclude a possibility that it may be observed with a lower dose.

### **3.2.2 Safety: Adverse event assessment in patients administered different doses of DEFINITY by bolus and infusion.**

#### **Missing data in ADE analysis**

**Missing data in cardiac monitoring of patients.** The sponsor provided a summary of ADEs by dose. However, there is a discrepancy between the actual data and the list submitted as an ADE summary. A large number of patients had a drug related QTc prolongation. The Sponsor referred to at least 5 such patients in the original submission and provided data on 4 more when an additional request was made. A line listing provided evidence for a total of at least 20 patients with a drug related, new-onset ECG change.

The ADE summary in the latest submission (March 13, 2000) describes only a total of 2 patients in the same dose category ( March 13, 2000 submission, Appendix G, New-Onset Adverse Experiences, p.52, Table 5, column 2). One ADE is listed under ECG ABNORMAL SPECIFIC and another under ECG ABNORMAL.

**Missing data in monitoring of normal volunteers.** 11/16 subjects who were administered placebo (described in MOR #1 (p.51), had a measured drop in diastolic blood pressure more than 20%. However, no ADE is listed as reported by the Sponsor under two general categories: CARDIOVASCULAR DISORDERS GENERAL (including hypotension) and HEART RATE

AND RHYTHM DISORDER ( March 13, 2000 submission, Appendix 3, New-Onset Adverse Experiences, Table 1 (pp. 034 and 036, column 1). It is unlikely that, a true placebo could elicit large drops (~~more than 20%~~) in both diastolic and systolic blood pressures as well as increases in pulse and respiratory rate in a large proportion of healthy young males. These rates were 69%, 25%, 56% and 62% for DBP, SBP, pulse and respiratory rate, respectively.) It is unlikely, that these changes, would result in only two cases of headache and one case of diarrhea (ADEs, March 13, 2000 submission, p.038).

#### **ADEs associated with placebo**

In Stedman's Medical Dictionary, 23<sup>rd</sup> edition, p. 1092 is placebo defined as 1. An indifferent substance, in the form of a medicine, given for the suggestive effect. 2. An inert compound, identical in appearance with material being tested in experimental research, where the patient and the physician may or may not know which is which.

In the studies with DEFINITY, the vehicle placebo, a mixture of phospholipids as liposomes was injected into the blood stream (mainly in normals). On the other hand, placebo as saline which is colorless and was used in patients, can not be considered identical in appearance with DEFINITY which is milky white. An investigator knew always whether he was injecting saline or DEFINITY.

Sixteen **normal volunteers** received the vehicle placebo (DEFINITY but without its gas component) were reported to exhibit only 3 ADEs. Namely, there were 2 cases of HEADACHE and 1 case of diarrhea (March 13, 2000 submission, pp. 034 –039, column 1). These could be considered occurring by chance only.

For 14 **patients** who received the same (DEFINITY but without its gas component) 9 ADEs were reported, but only HEADACHE and UPPER RESPIRATORY INFECTION occurred with the frequency greater than one (Submission March 13, 2000, p.38, column 2). These may be interrelated, but they might not have occurred by chance only. The remainder of ADEs (frequency <2) in this small group of patients could have happened by chance only.

Sixty-seven **patients** received **saline** as placebo (March 13, 2000 submission, pp. 33 – 43)) and only 4 ADEs were reported with a frequency greater than 1. These are HEADACHE (7), PARESTHESIA( 2), HYPERGLYCEMIA (2) and UPPER RESPIRATORY INFECTION (2).

#### **Conclusion:**

The results of ADE monitoring of placebos did not show any surprising or unexpected findings. Considering that 42/67 patients who received saline were elderly cardiac patients, some of these

findings such as dizziness, arrhythmia, tachycardia, asthma or dyspnea do not appear extraordinary. All of them were reported only once in a group of 67 patients.

#### **ADEs associated with bolus injection of DEFINITY.**

A dose response relationship is hard to discern throughout all the patients injected by bolus with DEFINITY (March 13, 2000 submission, pp. 051-059). The results confirmed the earlier assessment described in MOR #1. For the bolus administration:

- 1) There is no evidence of dose response relationship across the ADE categories.
- 2) No dose response relationship was established even for the categories which may be impacted by changes in multiple body systems such as DIZZINESS, NAUSEA or CHEST PAIN.

#### **ADEs associated with continuous infusion of DEFINITY.**

Compared to bolus administration there is about a 60% decrease in ADEs with infusion. However, an exception seems to be the QTc prolongation and related ECG changes. That question was addressed earlier in this review.

A dose response relationship appears absent for the patients infused with DEFINITY (March 13, 2000 submission, pp. 060-068). In this regard, the results largely confirmed the above assessment for bolus injection. For the DEFINITY continuous infusion:

- 1) There is no evidence of dose response relationship across the ADE categories.
  - a) HEADACHE, the ADEs associated with the cardiac system, NAUSEA, SKIN CHANGES, HYPERGLYCEMIA and DIARRHEA appear to occur more frequently with the smaller dose (up to 30 ul/Kg).
  - b) PLATELET, BLEEDING & CLOTTING DISORDERS, FLUSHING and BLOOD CELL DISORDERS are described more frequently with the larger dose (>30ul/Kg).

#### **Conclusion:**

1. The decrease in reported ADEs with continuous infusion, compared to the bolus injection, is about 60%, with a possible exception of ECG changes.
2. No evidence was found for a dose response relationship between DEFINITY and reported ADEs for both the bolus injection and continuous infusion.

#### **3.2.3 Safety: Pulse oximetry**

One patient in the study of oxygen saturation (232 patients had oxygen saturation measurements, but none within 3 min post dose) had a maximal post dose decrease in oxygen of 9% and another patient had an 8% decrease. The first patient had a 2% decrease



at 30 minutes after the second dose of DEFINITY, 9% at 10 minutes and 8% at 24 hrs. The second had an 8% decrease at 10 minutes (time interval between first and second dose was 28 to 50 min) and the oxygen saturation returned to baseline at 24 hrs. According to the Sponsor (Vol. 8, p. 75, first paragraph) both patients had cardiac illnesses, hypertension, were smokers, and one also had COPD.

None of these, however, can reasonably explain the finding of a sudden and long lasting decrease in oxygen saturation.

The magnitude of the drop in oxygen saturation, immediately following the dose, is unknown. The information may suggest whether or not an embolic event occurred. A prolonged desaturation may suggest the lasting consequences of an acute embolic event.

Also as described in this submission, two other patients had a decrease in oxygen saturation of 4% and 6%, respectively, at 15 min which resolved in 1 hr. No subjective adverse events were reported and recorded. One of these patients had a decrease in DBP of 19 mmHg and SBP of 20 mmHg and an increase in respiratory rate at 5 minutes. Changes in vital signs preceded the reported change in oxygen saturation suggesting the possibility of an earlier, immediately post-dose embolic event which remained undetected because lack of data obtained in a timely manner.

A patient who developed a response to DEFINITY had COPD, emphysema, chronic bronchitis, asthma and allergic sensitivities experienced a decrease in oxygen saturation by 5% at 5 minutes and 4% at 30 minutes and beyond. There was also a decrease in diastolic and systolic blood pressures and an increase in respiratory rate. This was explained by an allergy which resolved in 2 hrs.

The Sponsor asserted, that patients with COPD are no more prone to adverse drug events than the rest of the population.

**Conclusion:**

The value of oxygen saturation measurements in the DEFINITY studies lies primarily in those obtained immediately after the drug administration. The drop in oxygen saturation triggered a vital sign response. When a change of the vital signs is detected earlier than oxygen saturation, the drug effect is uncertain. It was found in the original NDA review that large numbers of normal volunteers (>60%) as well as patients (20% - 40%) had large drops in DBP (>20%) which started relatively early.

The essence of this comment in the approvable letter was the inability of this study to demonstrate the intended goal. Depending on reader and study, the improvement in the detection of wall motion abnormality due to DEFINITY ranged from 1% to 38%. The standard deviation for all reads ranged from 16 to 30.

The Sponsor attempted to reason (Vol. 8, p.1, last paragraph) that these results are sufficient for the efficacy claim. A point was made that there is a large inherent variability in the assessment of wall motion. However, this may not be entirely correct. The differentiation into 4 categories is not difficult for an experienced reader. *Normal* wall motion is characteristic for a healthy heart. In diseased heart, the wall motion may be reduced, *hypokinetic*, or entirely absent, *akinetic*, when individual segments are considered. When the diseased heart moves in an erratic, disorganized way it is assessed as *dyskinetic*. It is not particularly difficult to discern these 4 categories. Those were the only categories used by the blinded readers. With the gain by the injection of DEFINITY small and the standard deviation relatively large, the role of DEFINITY contrast enhancement in the clinical use for wall motion assessment remains unresolved.

The improvement in regard to variability among readers with DEFINITY, as opposed to the reads without DEFINITY, as suggested by the Sponsor (Vol. 8, p.2, par. 1) has no bearing on the fundamental question whether or not to approve the drug. The purpose of the drug is not to decrease or eliminate variability, but to see whether the heart is diseased, and how much. The Sponsor also implied that the results could be improved by a consensus read, but this option is impractical, since readers are not independent and the results of the combined read cannot serve as the primary image evaluation to demonstrate efficacy. Likewise, although it would be possible to classify the wall motion into 3 categories instead of 4 categories as it is currently done, and this would likely improve the results and decrease the variability among the blinded readers, the place of this approach in the clinical management of the patient would have to be demonstrated prior to approval. This seems impractical at this time.

**Conclusion:**

The Sponsor did not present any new evidence and the arguments in support of potential approval of this drug for the wall motion assessment are without merit at this time.

**Conclusion:**

The requested additional studies were not provided. The re-analysis submitted does not assure the general applicability of the results.

**4.1 Summation:**

The Sponsor provided a number of satisfactory answers to the Agency suggestions, but the critical points regarding safety and efficacy were not answered. The latter include data

1. on            for the wall motion,
2. on safety related to the size limit of the activated microbubble
3. on safety related to potential clumping, aggregation or coalescence of particles

The data on ECG changes in patients with QTc changes following DEFINITY confirms that DEFINITY is associated with significant cardiovascular toxicity, which remains not well characterized because of lack of data collected in timely manner.

**Regulatory:**

**Efficacy:**

The re-submission did not describe data to validate the use of DEFINITY in the evaluation of cardiac wall motion  
No additional studies were provided.

**Safety:**

1. Although numerous changes in manufacturing have been agreed to by the Sponsor, the activated microbubble upper limits of the particle size may still be unchanged. Its impact on safety was not tested satisfactorily in a dose ranging trial as requested in the Approvable letter of Oct. 9., 1999. No bridging study was planned at the time of re-submission. All these conditions for approval were not met.
2. One study was performed to characterize preclinical safety pharmacology and another to evaluate the potential clumping, aggregation or coalescence. Both studies had technical flaws, but only the study on clumping, aggregation or coalescence is deemed insufficient. Although the analyses provided by the Sponsor are of limited value because of omission of ~~numerous~~ eligible patients, the Sponsor concluded that 18.3% patients had a QTc prolongation. The Sponsor's analyses were at odds with this reviewer's findings which showed that about 10% of all cardiac patients entered into the study with DEFINITY exhibited ECG changes, including PVC, as related to a QTc prolongation. With these

limitations, the Action letter request in regard to ECG changes related to QTc prolongation was met.

3. Additional data were provided to complete the adverse risk assessment, including tables showing the effect of two "placebos" and a comparison of bolus and infusion administration. An approximately 60% decrease in ADEs with infusion, as compared with the bolus injection, was reported. The Action letter request was complied with.
4. The Action letter request was met in respect to initial characterization of the safety profile of 1.3 ml DEFINITY in 50 ml saline in echocardiography.
5. The Action letter request was fulfilled in regard to the reproductive studies with the final to-be-marketed formulation.

**Safety Update:**

The Sponsor requested a waiver from the pediatric labeling for DEFINITY under 64 FR 66632A and supplied the retabulation of safety data as outlined in the Action letter of Oct. 8, 1999. A single report of serious adverse drug event was also attached. All other questions were also responded to, however, they did not yield substantive information. The safety update is satisfactory, but the Sponsor's, reason for the omission of pediatric development, because a smaller number of studies may be ordered, is not valid. The Sponsor should submit a plan for pediatric development, as described in the Action letter of October 8, 1999.

**Scientific:**

1. This review confirms the earlier findings regarding this drug's effect on some of cardiac parameters. Approximately, 10% of all cardiac patients who underwent the study with DEFINITY experienced ECG changes, including PVCs, which may confer a significant risk of subsequent cardiac death.
2. No dose response relationship was found for the use of DEFINITY by bolus injection or continuous infusion judging by ADEs.
3. There is about a 60% decrease in ADEs with the use of infusion, but this may not apply to a QTc prolongation and related ECG changes. Large additional studies with the ECG monitoring performed in a timely manner are needed to exclude this possibility.
4. The evaluation of the safety profile continues unresolved because of the lack of data obtained in a timely manner.
- 5.

**5.1 Recommendation: APPROVABLE.**

CC: NDA Archive

HFD-160/ Division File

HFD-160/ T.Nguyen/Zolman

*[Signature]*  
Medical Officer

*7/11/00 I agree that this submission supports a recommendation of approval for Definity /S/ M.D.*